REMARKS

At the outset, it is noted that a shortened statutory response period of three (3) months was set in the July 2, 2008 Official Action. The initial due date for response, therefore, was November 2, 2008. A petition for a three (3) month extension of the response period is included with this amendment and request for reconsideration, which is being filed before the expiration of the three (3) month extension period.

It is also noted preliminarily that because no claim amendments are presented herewith, this response does not include a claim amendment section.

In the July 2, 2008 Official Action, claims 1-4 and 11-21 and 23 have again been rejected under 35 USC §103(a), as allegedly unpatentable over WO 99/33508 of Nitz et al., considered in view of Avis, Pharm. Dosage Forms, Vol. 1: Parenteral Medications, 173-175 (1992), which is referred to by the examiner as "DeLuca". The examiner maintains the position that the claimed compounds are structural isomers of the compounds disclosed in WO 99/33508 and, as such, would have been obvious to the artisan of ordinary skill. The examiner relies on Cammarata (Medical Chemistry, 15(6): 573-77 (1972)), a newly cited reference, as evidence allegedly establishing that ring walking is commonly practiced in the field of organic synthesis "in the hopes of identifying a structure with the greatest therapeutic properties". See page 3 of the July 2, 2008 Official Action. DeLuca is cited for its disclosure of useful carrier vehicles for parenteral formulations. According to the examiner, it would have been obvious to one of ordinary skill in the art, at the time the present invention was made, to combine the disclosures of WO 99/33508 and DeLuca, because in doing so one purportedly would create a pharmaceutically active formulation suitable for safe administration to a patient.

The July 2, 2008 Official Action also states that claim 22 is objected to as dependent on a rejected base claim, but would be allowable, if rewritten in independent form.

The foregoing rejection and the objection to claim 22 constitute all of the grounds set forth in the July 2, 2008 Official Action for refusing the present application.

The 35 USC §103 rejection of claims 1-4, 11-21 and 23 over the combined disclosures of WO 99/33508 and DeLuca cannot properly be maintained in view of the evidence of unexpected results presented in the Declaration of Christopher J. Burns submitted herewith.

The assessment of patentability under 35 USC §103 requires consideration of the differences, whatever their nature, between the subject matter sought to be patented and the

prior art, and the determination of whether the claimed subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *In re Krazinski*, 146 USPQ 25, 31 (CCPA 1965). When a patent is sought on chemical compounds, the "subject matter as a whole" includes not only the structural formula, but all of the properties of the claimed compounds, as well. *In re Wiechert*, 152 USPQ 347 (CCPA 1967).

At page 7 of the July 2, 2008 Official Action, the examiner asserts that:

> The instantly claimed compound[s] are obvious as they are structural isomers of reference '508 and one of ordinary skill in the art would be motivated to make such modifications with the expectation that the compounds and compositions thereof would possess identical pharmacological properties as those taught by the reference.

Indeed, the concept of *prima facie* obviousness is based on the expectation that compounds which are very similar in structure will have similar properties. *In re Hoch*, 166 USPQ 406, 409 (CCPA 1970). Accordingly, to overcome the *prima facie* case, it must be shown that the expectation on which it is based is in fact unsound, as by showing there are substantial, actual differences in properties. *Id.*

In the present case, applicants have found, unexpectedly, that the solubility characteristics of the meta-substituted bis-tetrazol-benzyhydrylphenols claimed in this application are far superior to the corresponding para-substituted compounds in solvent systems customarily used in electrohydrodynamic (EHD) delivery devices for pulmonary administration to patients suffering from pneumovirus infection. As pointed out at page 5 of the present specification, "[t]he improved solubility of the compound of Formula I in the formulations used in an EHD device facilitates the delivery of higher concentrations of the desired compound to the patient pulmonary tissue with fewer numbers of actuations of the EHD device".

The experimental data supporting this unexpected finding is set forth in Table 2 at page 85 of the present specification. The data show a substantial increase in solubility for the meta-substituted compounds in comparison to the corresponding para-substituted compounds with the former being from about 2.5 to about 23 times more soluble than the latter.

The technique known as "ring walking", although commonly used in the drug discovery process, simply facilitates the optimization of desirable drug properties. It does not

enable the prediction of such properties.

The improved solubility characteristics exhibited by the compounds of the present invention affords a distinct practical advantage over the compounds described in WO 99/33508. Specifically, the para-substituted compounds of WO 99/33508 are only poorly soluble in the EtOH:PG:H_2O formulation of the type utilized for EHD delivery of pulmonary drugs. For example, the compound of Example 1 in WO 99/33508 is stably soluble in the formulation at 200 μg/mL, thus limiting the deliverable quantity of drug to approximately 4 μg per actuation of the device. This is about 10 times less than the anticipated therapeutic dose, and so would require 10 actuations of the device to deliver the desired dose. This is plainly impractical and would result in low patient compliance, thereby reducing the clinical benefit. The surprising improvement in solubility in the EtOH:PG:H_2O formulation observed for the meta-substituted compounds of the present invention, by contrast, allows for a single actuation to deliver the desired therapeutic dose.

The same solubility data set forth at page 85 of the present specification is included in the Declaration of Christopher J. Burns submitted herewith. As such, it is evidence that must be taken into account in determining the patentability of applicants' invention. *In re Wiechert, supra; In re Ward*, 141 USPQ 227 (CCPA 1964).

Dr. Burns Declaration includes additional solubility data showing that the meta-substituted bis-tetrazole-benzhydrylphenols claimed in this application are substantially more soluble in a conventional EHD carrier solvent (85% EtOH: 5% H_2O: 10% PG) than in water. See Table 1 of the Declaration.

In his Declaration, Dr. Burns avers that the solubility differences between the respective test compounds are substantial (¶ 10), that such differences have important practical advantages regarding clinical utility (¶ 11) and that the differences were unexpected (¶ 11).

Dr. Burns Declaration further points out that aqueous formulations of the compounds claimed by applicants herein were unsatisfactory for inhaled drug delivery using a nebulizer, EHD device or the like (¶ 9).

Dr. Burns ultimately concludes that the improved solubility exhibited by the meta-substituted bis-tetrazole-benzhydrylphenols renders those compounds "clinically useful for delivery in aerosol form by an inhaler device, whereas the corresponding para-isomers could not be practically delivered by that route of administration" (¶ 14).

Although the Declaration of Dr. Burns addresses the unexpected benefits obtainable when the claimed compounds are used in a specific route of administration, it is unnecessary

for the claims to be limited to the specific utility relied on as evidence of patentability. *In re Ward, supra.* To the same effect is *Ex parte Schibler*, 131 USPQ 234 (Bd. Apps. 1961).

The artisan of ordinary skill would not find in DeLuca any useful guidance that pertains to pneumovirus drug formulations for delivery by inhalation, and certainly not the advantage to be gained in this connection by administering the meta-substituted compounds of the present invention, as compared to the para-substituted compounds of WO 99/33508. DeLuca teaches only general principles concerning one particular mode of parenteral drug delivery, i.e., drug preparations for administration by hypodermic injection.

In summary, where, as in this case, there exists a substantial, advantageous, unexpected difference between the compounds claimed by applicants and those of the prior art, any question as to the obviousness of the claimed compounds must be resolved in favor of their patentability. *In re Lunsford*, 148 USPQ 716 (CCPA 1966) (meta- and para-substituted anti-convulsant phenoxymethyl-oxazolidones held patentable over corresponding ortho-isomer based on a significant difference in potency).

In view of the Declaration of Christopher J. Burns and the foregoing remarks, it is respectfully urged that the rejection and objection set forth in the July 2, 2008 Official action be withdrawn and that this application be passed to issue, and such action is earnestly solicited.

Respectfully submitted,

DANN DORFMAN HERRELL and SKILLMAN, P.C.

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of	:
	: Docket No. 1282-P02956US01
David J. RYS et al.	:
	: Confirmation No.: 6431
U.S. Appln. No. 10/524,313	:
	: Examiner: Kyle A. Purdy
Filed: July 15, 2005	:
	: Group Art Unit: 1611
For: COMPOUNDS, COMPOSITIONS AND METHODS FOR TREATING OR PREVENTING PNEUMOVIRUS INFECTION AND ASSOCIATED DISEASES	:

Commissioner for Patents
Alexandria, Virginia 22313-1450

DECLARATION OF CHRISTOPHER J. BURNS

Sir:

I, Christopher J. Burns, Ph.D., hereby declare as follows:

1. I am a joint inventor of the invention, "Compounds, Compositions and Methods for Treating or Preventing Pneumovirus Infection and Associated Diseases", described and claimed in the above-identified patent application (hereinafter "the '313 application").

2. My scientific background follows: I graduated with a BS in chemistry (*summa cum laude*) from St. Joseph's University in 1984, and then received a Ph.D. in organic chemistry from the Massachusetts Institute of Technology in 1989 under the mentorship of Prof. K. Barry Sharpless. I have worked since 1989 in the pharmaceutical industry in drug discovery and development, specializing in medicinal chemistry. I worked for Rhone-Poulenc Rorer/Aventis for 12 years in research projects directed at drug discovery in bone metabolism, oncology, inflammation, and cardiovascular disease. I worked for 3 years as Head of Chemistry at ViroPharma, Incorporated in drug discovery

directed against new antiviral agents. Since 2004 I have worked as Vice President of Research at Protez Pharmaceuticals, an antibacterial-based drug discovery and development company. My *curriculum vitae* accompanies this declaration.

3. I do not have any financial or other beneficial interest in the invention which is the subject of the '313 application, the application itself or any patent that may be issued thereon, or in any entity that holds rights in the aforementioned invention, patent application or patent.

4. In addition to having over 19 years experience in the field of drug discovery and development, I am the author or co-author of more than 25 scientific journal articles and abstracts on the subject of drug discovery. I am also named as sole or joint inventor in more than 15 issued patents or pending patent applications. A list of my patent and non-patent publications is included in my attached *curriculum vitae*.

5. I have served as an expert reviewer on various NIH scientific panels around antiviral and antibacterial agents. I am not currently consulting.

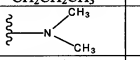
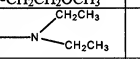
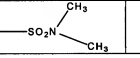
6. As a named joint inventor, I have read and am familiar with the subject matter of the '313 application, and I have reviewed the Official Action dated July 2, 2008 in the '313 application.

7. Based on my review of the July 2, 2008 Official Action, I understand the examiner to have rejected claims 1-4, 11-21 and 23 as allegedly obvious based on the disclosures of WO 99/33508 of Nitz et al., which describes certain bis-tetrazole-benzhydrylphenols having anti-pneumovirus activity, and Pharm. Dosage Forms, Vol. 1:

Parenteral Methods, K. Avis ed., Marcel Dekker, pp. 173-175 (1992), which is referred to in the Official Action as "DeLuca et al.". In support of this ground of rejection, the examiner asserts that it would have been obvious to one of ordinary skill in the art, at the time the invention of the '313 application was made, to combine the teachings of Nitz et al. and DeLuca et al., so as to create a pharmaceutically active formulation suitable for safe administration to a patient. The examiner further asserts that the claimed compounds are obvious as they are structural isomers of Nitz et al. and one of ordinary skill in the art would be motivated to make such modifications with the expectation that the compounds and compositions thereof would possess identical pharmacological properties as those taught by Nitz et al. As for the carrier medium, it is the examiner's position that the use of water, ethanol and/or propylene glycol as the carrier medium is suggested by statements in Nitz et al. to the effect that all pharmaceutically acceptable carrier mediums can be used to carry the drugs. According to the examiner, this statement would motivate one to look to the prior art of drug formulations, where solvents such as water, ethanol and propylene glycol are commonly used as a carrier medium.

8. I have been requested to describe the outcome of certain testing that was conducted under my direction and supervision, comparing the solubility properties of compounds having the structural formula of claim 1 of the '313 application with the corresponding para-substituted isomers. The purpose of the testing was to assess the suitability of the test compounds for delivery in atomized form using an inhalation device. To that end, each test compound was formulated in an ethanolic carrier medium which is commonly used in an electrohydrodynamic (EHD) inhaler device. These test results are set forth in Table 1 below.

TABLE 1

Example Number	R_1	Meta Position Solubility (mg/mL)	Para Position Solubility (mg/mL)
1	$-CH_2CH_2CH_3$	1.9	0.18
2		2.10	0.09
6	$-OCH_2CH_3$	1.85	0.30
16	$-CH_2CH_2OCH_3$	1.14	0.29
20		1.45	0.21
27	$-NO_2$	0.98	0.16
31		0.08	0.03

9. In previous testing of the same compounds as aqueous formulations, it was found that such formulations were unsatisfactory for inhaled drug delivery, using a nebulizer, EHD device or the like.

10. The test results set forth in Table 1 show that the meta-substituted bis-tetrazole-benzhydrylphenols, having the structural formula of claim 1 of the '313 application, are uniformly more soluble in the ethanolic carrier medium than the corresponding para-isomers, the former being about 2.5 to about 23 times more soluble than the latter. By contrast, the water solubility of the respective isomers is quite similar.

11. The solubility differences shown in the foregoing test results were unexpected. Furthermore, these differences have important practical significance due to the limited quantity of drug which is deliverable per actuation of the devices

conventionally used for inhaled drug delivery. For example, the meta-isomer of test compound 6 in Table 1 would be deliverable at a dose of approximately 40 μg per actuation of an EHD device, which is the anticipated therapeutic dose for this compound. The corresponding para-isomer, on the other hand, would be deliverable at a dose of only about 6 μg per actuation of an EHD inhaler device, and thus would require approximately 7 actuations in order to deliver the anticipated therapeutic dose. The requirement of 7 actuations to deliver a dose would result in lower patient compliance and reduced clinical benefit.

12. The foregoing test data demonstrates that the superior solubility exhibited by the meta-isomers, as compared to the corresponding para-isomers, produces a substantially improved result with respect to the potential clinical utility of the compounds claimed in the '313 application when delivered via an inhalation device.

13. Additional solubility testing was performed on other compounds having the structural formula of claim 1 of the '313 application. In these tests, the solubility of meta-isomers in an ethanolic carrier medium was compared to the solubility of the same compound in water. The compound of Example 1 of WO 99/33508 was included in this test as a basis of comparison. The results of the testing, which are set forth in Table 2, below, show that the solubility of each of the meta-isomers in an ethanolic carrier medium is substantially greater than its solubility in water, whereas the solubility of the reference compound from WO 99/33508 in the respective carrier media is essentially the same. Furthermore, in six out of the eight meta-isomers tested, the increase in solubility was sufficiently substantial that the amount of such compounds deliverable using an EHD inhaler device, for example, would provide a therapeutic dose.

TABLE 2

Example Number	R_1	Average Concentration (μg/mL) 85:5:10 (EtOH:H_2O:PG)	Average Concentration (μg/mL) H_2O
Reference Cmpd	4-OH	132.39 (151.8, 112.98)	123.80 (112.98, 135.40)
5	3-OCH_3	579.26 (378.82, 779.70)	242.47 (200.69, 284.24)
9	3-$CH_2CH(CH_2CH_3)_2$	1011.63 (910.36, 1112.90)	418.84 (311.14, 526.54)
10	3-cyclohexyl	621.82 (663.62, 580.01)	46.01 (73.97, 18.05)
11	3-$CH_2CH_2CH_2CH_3$	2965.65 (3065.80, 2865.60)	233.87 (306.88, 160.86)
13	3-$CH_2CH_2CH_2$ CH_2CH_3	2731.05 (2614.10, 2848.00)	282.76 (144.04, 421.48)
14	3-$CH(CH_3)CH_2CH_3$	2579.25 (2868.10, 2290.40)	181.65 (264.24, 99.06)
15	3-$CH_2CH(CH_3)_2$	1729.20 (1733.90, 1724.50)	167.79 (166.92, 168.66)
34	NHAc	1141.90 (1102.70, 1181.10)	206.17 (257.14, 155.20)

14. Although the solubility test results shown in Tables 1 and 2, above, were carried out using an ethanolic carrier medium that is in common use in EHD inhaler devices, it is my view, based on almost 20 years experience in the field of drug discovery and development that the compounds having the structural formula of claim 1 of the '313 application would exhibit improved solubility, relative to the corresponding para-isomers, in ethanolic solvents generally. Such improved solubility makes the compounds having the structural formula claimed in claim 1 of the '313 application clinically useful for delivery in aerosol form by an inhaler device, whereas the corresponding para-isomers could not be practically delivered by that route of administration.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the '313 application or any patent issued thereon.

12/7/08
Date

Christopher J. Burns

Christopher J. Burns, Ph.D.

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EDUCATION

Massachusetts Institute of Technology, Cambridge, MA
Ph.D. in Organic Chemistry (May, 1989)
Dissertation: "Studies on Asymmetric Oxidation Reactions Using Titanium and Osmium Catalysts". Advisor: Professor K. Barry Sharpless

Saint Joseph's University, Philadelphia, PA
B.S. in Chemistry (June, 1984)
Summa Cum Laude (GPA = 3.94/4.0)

EXPERIENCE

Protez Pharmaceuticals – Antibacterial Company (subsidiary of Novartis)

Vice President, Research (2004-Present)

- Member of Senior Management Team, reporting to the CEO.
- Responsible for the strategy and execution of internal and external research initiatives on core antibacterial technologies (beta-lactamase inhibitors, bactericidal potentiators of known antibiotics, novel anti-biofilm agents, novel biodefense agents).
- Management of internal and external chemistry, biology, DMPK research – total FTE reach >20 FTEs.
- Principal Investigator on 3-year $3.5MM U01 Biodefense grant (novel inhibitors of *Bacillus anthracis* (anthrax))
- Key role in successful venture capital fund raising ($21MM, Series B) with responsibility for managing Protez Research budget

ViroPharma Incorporated – Antiviral Biopharmaceutical Company (NASD: VPHM)

Director, Chemistry (2001-2004)

- Managed department of 33 scientists (Medicinal Chemistry, Molecular Modeling, Early Scale-up)
- Co-managed Discovery budget ($12-14M annual)
- Member Joint Management Team and Joint Steering Committee for Hepatitis C Alliance with Wyeth Pharmaceuticals
- Core Member ViroPharma R&D Management Team
- Co-responsibility for designing and executing Discovery strategic approaches

- Member of in-license and out-license business development team

Key achievements

- Hepatitis C. Three novel replication inhibitor clinical candidates (in 2 chemical series) progressed into Development (Alliance with Wyeth Pharmaceuticals) – INDs filed and clinical trials initiated for HCV-371, HCV-086, and HCV-796. HCV-796, a first-in-class non-nucleoside HCV RNA polymerase inhibitor, successfully achieved proof-of-concept in human monotherapy and combination therapy.
- Respiratory Syncytial Virus (RSV). Novel inhibitors of RSV fusion protein discovered. VP 17470 progressed into Preclinical Development.
- Category A (Biodefense) Viruses.
    1. Smallpox. Novel smallpox egress inhibitors discovered. VP-246 (now renamed ST-246) progressed into development – licensed to SIGA Technologies. Compound satisfies animal efficacy rule and is currently in late-stage clinical development.
    2. Hemorrhagic Fever Viruses. Novel inhibitors of category A (Biodefense) viruses discovered and progressed (collaboration with USAMRIID) – IP estate licensed to SIGA Pharmaceuticals. 3 SBIR Phase I grants awarded (total $2.9MM); 2 SBIR Phase II grants awarded (total $16MM)

Rhône-Poulenc Rorer/Aventis - Department of Medicinal Chemistry (1989-2000)

Department Director (1998-2000) - Cardiovascular/Antithrombosis research

- Representative of U.S. Chemistry (RPR) in HMR/RPR merger integration task force
- Managed team of 20 scientists (Medicinal Chemistry, Computer-Assisted Drug Design (CADD) group)
- Co-managed U.S. Medicinal Chemistry budget ($10M annual)
- Core Member of Global Lead Optimization Committee (7 Members across 3 worldwide research sites) – responsible for monthly project review of all Lead Optimization projects across 6 therapeutic areas
- Inhibitors of serine proteases implicated in venous and arterial thrombosis discovered – one compound progressed into formal Preclinical Development
- Novel modulators of nuclear receptor action for dyslipidemia discovered

Department Manager (1996-1997) - Bone Metabolism research

- Managed team of 12 medicinal chemists – research directed at anabolic therapies for treatment of osteoporosis
- Proprietary PTH analog discovered and progressed into Preclinical Development
- Methods developed for combinatorial libraries biased toward 7-transmembrane G-protein-coupled receptors ("privileged" substructure approach)

Section Manager (1994-1996) - Asthma/Inflammation research

- Managed team of 7 medicinal chemists – research directed at inhibition of pro-inflammatory cytokines and matrix degradative enzymes (projects directed at PDE4,

TNF-α release, and matrix metalloproteinases)
- Novel series developed capable of selective or dual PDE4/MMP inhibitory activity

Principal Investigator (1993-1994) - Oncology research (expatriation in Paris, France)
- Managed team of 5 medicinal chemists
- Novel inhibitors of farnesyltransferase discovered and optimized

Senior Research Scientist (1991-1993) - Bone Metabolism research
Research Scientist (1989-1991)
Research directed at antiresorptive therapies for osteoporosis
- Supervised one Associate Chemist
- Novel bisphosphonate mimetics discovered with high bone affinity

Massachusetts Institute of Technology (1984-1989)

Graduate (Ph.D.) studies with Prof. K. Barry Sharpless
- Osmium- and titanium-catalyzed asymmetric methodology

E. I. duPont de Nemours (Summers, 1982-84)

Summer internships (Marshall Research Labs, Philadelphia, PA)
- Organic and polymer chemistry research

PUBLICATIONS/PRESENTATIONS/PATENTS

Antiviral Research (ViroPharma Incorporated)

Discovery of HCV-796: A potent and orally bioavailable hepatitis-C polymerase inhibitor under clinical development. Saha, Ashis K.; Young, C.; Del Vecchio, A. M.; Bailey, T. A.; Reinhardt, J. A.; Kulkarni, B. A.; Faitg, T. H.; Feng, H.; Rippin, S. R.; Blackledge, C. W.; Rys, D. J.; Lessen, T. A.; Swestock, J.; Deng, Y.; Nitz, T. J.; Chunduru, S.; Chopra, R.; Collett, M.; Pevear, D.; Howe, A. Y. M.; O'Connell, J.; Mansour, T.; Burns, C. J.. Abstracts of Papers, 233rd ACS National Meeting, Chicago, IL, United States, March 25-29, 2007, MEDI-238.

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An orally bioavailable antipoxvirus compound (ST-246) inhibits extracellular virus formation and protects mice from lethal orthopoxvirus challenge. Yang, Guang; Pevear, Daniel C.; Davies, Marc H.; Collett, Marc S.; Bailey, Tom; Rippen, Susan; Barone, Linda; Burns, Chris; Rhodes, Gerry; Tohan, Sanjeev; Huggins, John W.; Baker, Robert O.; Buller, R. L. Mark; Touchette, Erin; Waller, Kem; Schriewer, Jill; Neyts, Johan; DeClercq, Erik; Jones, Kevin; Hruby, Dennis; Jordan, Robert. *J. Virology* **2005**, *79(20)*, 13139-13149.

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